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Review Article

Role of SOX family of transcription factors in central nervous system tumors

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Abstract: *SOX* genes are developmental regulators with functions in the instruction of cell fate and maintenance of progenitor's identity during embryogenesis. They play additional roles during tissue homeostasis and regeneration in adults particularly in the Central Nervous System (CNS). In the last years a growing number of evidences has shown that mutations and dysfunction of SOX factors are implicated in several human diseases, including a variety of cancers. In this review, we will summarize the current knowledge about SOX family in CNS tumors and their role in the origin and maintenance of the subpopulation of cancer stem cells in these tumors.

Keywords: SOX, CNS tumors, glioblastoma, glioma stem cell, cell of origin, oncogenic SOX2, therapy target

SOX family introduction

SOX (Sex-determining region Y (SRY)-box protein) family members are characterized by a conserved high mobility group (HMG) DNA-binding domain [1]. There are, at least, 20 members divided into 8 groups (from A to H), based on their HMG sequence identity in humans [2]. Members within a group preserve higher than 80% identity in their HMG-domain and share other well-conserved regions [3]. In addition, they share biochemical properties, have overlapping expression patterns and perform synergistic or redundant functions. In contrast, members from different groups usually perform different functions. *SOX* genes are developmental regulators with functions in sex determination, chondrogenesis, hematopoiesis, neural crest development and neurogenesis [4]. SOXB1, SOXB2, and SOXE members have a role in the instruction of cell fate and maintenance of progenitor's identity during embryogenesis. They are also important for stem cell maintenance and play additional roles during tissue homeostasis and regeneration in adults particularly in the CNS [5]. In the last years a growing number of evidences have shown that mutations and dysfunction of SOX factors are implicated in several human diseases, including a variety of cancers [6]. These diseases are originated in tissues overlapping with their expression pattern during embryonic development. Since SOX factors play an integral role in the maintenance of neural stem cells and in the specification and differentiation of neurons, astrocytes and oligodendrocytes, it seems reasonable to surmise that aberrant expression of members of this family is implicated in the development and maintenance of CNS tumors.

Central nervous system tumors

Tumors of the CNS consist of a heterogeneous group of neoplasias accounting for around 3% of the total number but representing 7% of deaths caused by cancer. Every year in the world, approximately 350.000 people are diagnosed with gliomas, making it the most common primary brain tumor (IARC http://globocan.iarc.fr, accessed on day/month/year). Gliomas display histological similarities to glial cells and according to which cell they most resemble, the World Health Organization (WHO) classifies them into astrocytoma, oligodendroglioma, ependymoma or mixed oligoastrocytoma. This classification is based solely on morphology. Based on histopathological and clinical criteria

they are classified into four classes of malignancy [7].

Glioblastoma multiforme (GBM) belongs to grade IV and accounts for 80% of the total primary malignant brain tumors in adults. The incidence ranges from 5 to 20 cases per 100,000 people per year [8] with an associated median survival of 15 months [9]. This survival identifies GBM as one of the most aggressive and fatal cancer overall.

The clinical hallmarks of GBM are its aggressive growth and inexorable recurrence as a consequence of the resistance to apoptosis, genomic instability and poor response to therapy [10]. It is also characterized for the presence of necrotic areas, for being highly invasive, infiltrative and with intense angiogenesis. In the last years different GBM characterizations have emerged based on the molecular knowledge of the genome [11-14] and transcriptome [15, 16]. These studies have provided a high-resolution picture of the GBM landscape uncovering the major structural genomic and expression alterations that may drive disease pathogenesis and biology. These comprehensive data sets reveal GBM as a heterogeneous collection of distinct diseases with multiple dependencies both within and across each particular subtype. Contributing to this grim picture is the fact that despite a huge effort to understand this disease and to develop effective therapies over the past few decades, there are still no such agents [17].

CNS tumors constitute the largest group of solid neoplasms of childhood and the ones that cause the highest mortality rates in this group age [18]. Because the developing brain is highly vulnerable to treatment-induced cognitive and endocrine sequelae, particularly from radiotherapy, ongoing studies are focusing on improving the duration and the quality of survival, in affected patients [18]. Medulloblastoma (MB) is the most common pediatric brain cancer and the treatment of patients with this disease poses an additional problem. Current therapies for MB cause dramatic impairment of cognitive function and predispose patients to future treatment-associated neoplasms [19]. Pediatric high-grade gliomas (pHGG) including diffuse intrinsic pontine glioma (DIPGs) comprise 15% to 20% of all childhood tumors of the CNS, and more than 70% of patients die within 2 years of diagnosis. Consequently, understanding the molecular circuitries underlying the development of pHGG is crucial to identify relevant therapeutic targets [20] for these neoplasms.

The cellular origin of CNS tumors

For many years, cancer has been based on a stochastic model, which considers that all cells within the tumor are highly proliferative, possess tumorigenic potential and are capable of tumor progression and repopulation. In the last decade, the demonstration that cancers are heterogeneous masses containing a hierarchy of cells has modified the original model [21]. This new theory postulates that a small subpopulation of cancer cells (called cancer stem cells, CSCs) drives tumor formation, growth, metastasis and resistance to therapeutic treatments [22]. There is compelling evidence in support of its existence in hematological malignancies and in numerous solid epithelial types of cancer including GBM and medulloblastoma [23]. In the brain, the CSCs population display Neural Stem Cells (NSCs) characteristics; unlimited proliferation, self-renewal potential and multipotency to differentiate into astrocytes, oligodendrocytes and neurons (**Figure 1**). Furthermore, these cells form tumors phenotypically similar to the original human ones when injected into the brain of immunodeficient mice, indicative of being responsible for the initiation and maintenance of adult and pediatric brain tumors [24-26]. CSCs display much greater tumorigenic potential than matched non-stem tumor cells, have the ability to migrate and are more resistant to apoptosis and therapy suggesting that these cells are also responsible for tumor relapses particularly in GBM cases [27].

The demonstration of functional neurogenesis in the adult brain [28, 29], the observation of a population with stem cells properties within the tumor bulk, opened the debate regarding the putative cell of origin of CNS tumors and postulated NSCs as the putative cell of origin for CNS tumors, mainly gliomas. Indeed, different genetic models have revealed that inactivation of p53/Rb/Pten/Nf1 tumor suppressors or enhancement in EGFR/PDGFR/PI3K oncogenic pathways in NSCs serve as glioma source [30, 31]. Intriguingly, different studies have demonstrated that targeting the same pathways in

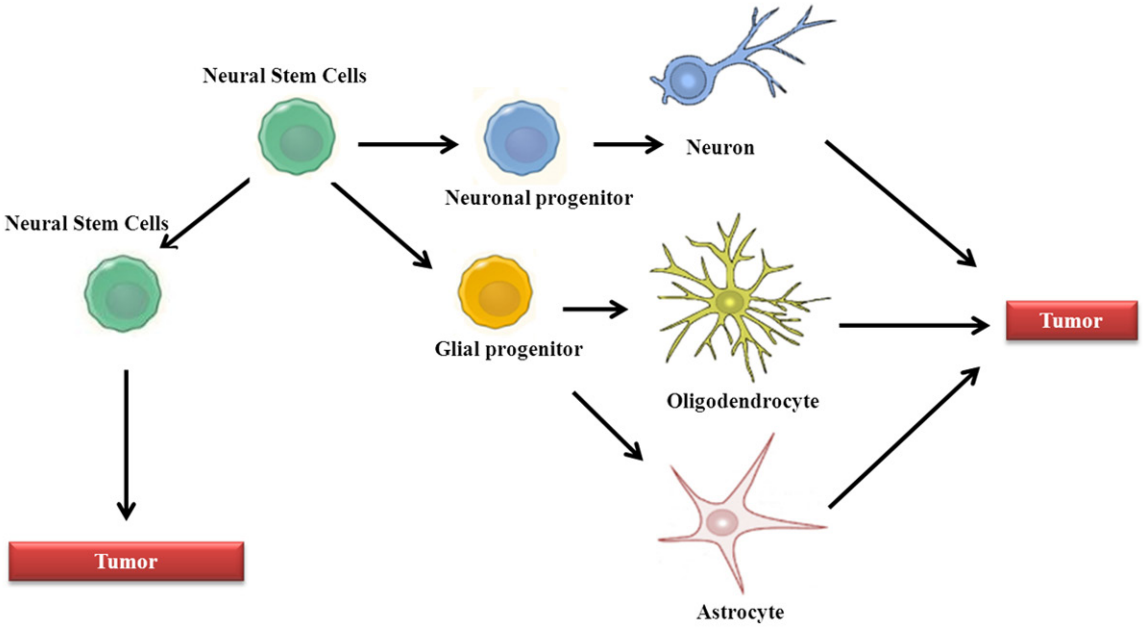

Figure 1. Glioma cell of origin and glioma stem cell (GSC) evolution. Normal cellular hierarchy comprises neural stem cells that progressively produce new stem cells and more restricted progenitor cells, finally yielding oligodendrocytes, astrocytes and neurons. Accumulation of genetic mutations in different cell types is sufficient to induce gliomas. These gliomas contain a population of GSCs with self-renewal capacity and ability to differentiate to all the lineages.

astrocytes, oligodendrocyte progenitors and neurons is sufficient to undergo oncogenic transformation and form malignant gliomas [32-34]. These evidences strongly indicate that glioma cell of origin is diverse probably explaining the complex and heterogeneous pathology, morphology and clinic that characterize this type of tumor (**Figure 1**).

The concept of CSC may have profound implications from the point of view of therapy in that expose this population as a crucial target [35]. Therefore dysregulation of pathways controlling normal NSCs could constitute a requirement for cancer development and might play predominant roles in CSCs too. For example Notch is required from the transition from primitive to definitive NSC and their maintenance. Aberration in Notch pathway results in tumor formation and its expression is deregulated in GBM [36, 37]. Sonic Hedgehog (SHH) pathway is required for neural stem/progenitor cell maintenance promoting their proliferation and self-renewal [38] and this pathway is also found deregulated in GBM [39]. Furthermore, a recent elegant study has demonstrated how developmental and regional differences influence neoplastic transformation in the CNS [40]. Thus, an active N-Myc mutant (T58A) generates medulloblastoma/primitive neuroectodermal tumors when transduced in cerebellar and brain stem NSCs, whereas develops diffuse glioma in forebrain NSCs. Tumors generated from diverse regions display different gene expression pattern including SHH dependence and independence within tumors from embryonic versus postnatal cerebellar NSCs [40]. Sox family members are critical transcription regulators of embryonic and neural stem cells, which are aberrantly expressed in several human cancers including GBMs. We plan to discuss, further down, their role in the development of the CNS and the implication of its deregulation in CNS tumors with particular attention in glioblastoma (**Figure 2**).

SOX2

SOX2 is a member of the SOXB1 (together with SOX1 and SOX3) required for the maintenance of the early embryo, before implantation [41]. SOXB1 group members are coexpressed in the neuroepithelium and show certain degree of functional redundancy in the developing CNS [41]. In particular, SOX2 is one of the four essential factors required for induced pluripo-

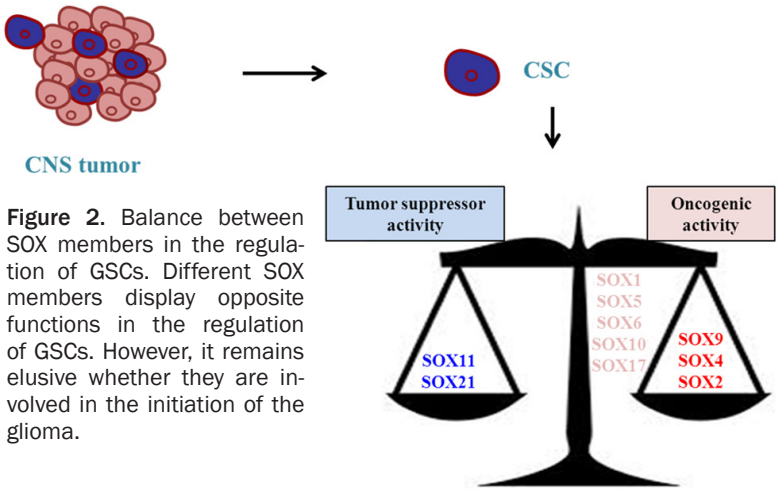

Figure 2. Balance between SOX members in the regulation of GSCs. Different SOX members display opposite functions in the regulation of GSCs. However, it remains elusive whether they are involved in the initiation of the glioma.

tent stem (iPS) cell induction [42]. It is widely expressed in the embryo, in particular in the developing CNS where its expression is initiated concomitant with the acquisition of neural progenitor identity and it functions to maintain it [1, 43, 44]. In the adult, its expression is maintained in different populations of stem cells [45-48], acting intrinsically to confer stem cell properties, but also more broadly by regulating the expression of critical niche factors as observed in the CNS [49].

SOX2 and GBM

SOX2 is highly expressed in several human cancers [50], including GBM [51-53]. Interestingly, the expression of SOX2 and other stem cell markers identifies a subset of patients with the poorest clinical outcome highlighting the clinical relevance of SOX2 in GBM and in several other neoplasms [54].

Functionally, SOX2 is enriched in human-derived glioma stem cells (GSCs) where it sustains stemness properties and maintenance of tumorigenicity [55, 56]. Indeed, siRNA-mediated downregulation of *SOX2* in GSCs impaired proliferation and their ability to form tumors *in vivo* [55]. SOX2 maintains GSC stemness using the same molecular targets of normal NSCs [55], supporting a hierarchical model of GBM controlled by SOX2 and opening the approach to find downstream genes as therapeutic targets. Furthermore, elevated expression of SOX2 is essential but not sufficient for maintaining the self-renewal of GSCs [53] indicating that other factors cooperate to activate stem cell-like properties. Supporting this notion, just recently Suva et al identified a core set of neurodevelopmental transcription factors (TFs) (POU3F2, SOX2, SALL2, and OLIG2) essential for GBM propagation. These TFs coordinately bind and activate stem-like tumor propagating cells (TPCs)-specific regulatory elements and are sufficient to fully reprogram differentiated GBM cells to "induced" TPCs, recapitulating the epigenetic landscape and phenotype of native TPCs [57]. In addition, SOX2 drives additional cancer-associated phenotypes and SOX2-driven malignant GSCs are highly invasive and have migratory characteristics [53], mimicking those of NSCs [58]. Indeed, SOX2 depletion induced attenuated cell proliferation is caused by decreased levels of Cyclin D1 [59], while the impaired invasive activity is mediated by inhibition of focal adhesion kinase (FAK) signaling and downstream proteins such as HEF1/NEDD9 and matrix metalloproteinases 1 and 2 [59].

In the last years the mechanism of *SOX2* activation in GBM has started to be unraveled. Our group identified *SOX2* gene amplification and promoter DNA hypomethylation in a set of GBM patients as the leading mechanism responsible for SOX2 aberrant expression [53]. SOX2 presents a high CpG density throughout the promoter that may poise the gene for repression upon differentiation [60], suggesting that *SOX2* promoter hypomethylation in GBM might reflect a more primitive cellular state resembling that found in NSCs [60]. SOX2 is also regulated transcriptionally and acts downstream relevant pathways in GBM formation. TGF-β regulates GSCs through SOX2 [56]. PDGF also modulates SOX2 activity. In fact, transforming activity of PDGF in neural progenitors and PDGF-dependent tumors in mice triggered *SOX2* expression [61]. In human GSCs, siRNA-induced downregulation of *SOX2* confers sensitivity to treatment with PDGF and IGF1 receptor inhibitors [62] suggesting that resistance to PDGF and IGF1-receptor inhibitors in GBM are related to SOX2 expression. Moreover, SOX2 is activated at translational level by eukaryotic initiation

Figure 3. SOX2 functions in tissue homeostasis and cancer. *SOX2* is emerging as a very complex factor with multiple functions. Here we include the most relevant for glioma.

factor 4E (eIF4E) [63]. Indeed, there is a positive correlation between SOX2 and eIF4E in GBM human samples and down-regulation of eIF4E decreases SOX2 protein level without altering its mRNA level in GSCs. Post-transcriptionally, different miRNAs including miR-9, miR-145, miR-21, miR-137 regulate GSCs and impart chemoresistance regulating SOX2 activity [64-67].

In order to address downstream targets of SOX2, microarray analyses identified 489 genes and 105 precursor microRNAs whose expression is altered in response to SOX2 silencing [68]. Among the relevant identified targets, BEX1 and BEX2 tumor suppressors and miR-143, miR-145, miR-253-5p and miR-452 are downregulated with SOX2 knockdown. Interestingly, in this study they found that SOX2 and miR-145 form a double negative feedback loop [68]. It is known that *miR-145* acts to silence multiple pluripotency factors, including SOX2, [69] during the switch from self-renewal to lineage commitment. Therefore it might be a mechanism to regulate the balance between an undifferentiated and committed state. However, this regulation warrants further investigation to determine their putative function in GBM.

In a very elegant study conducted by the group of Dr. Silvia Nicolis they address the question whether Sox2 was required by oligodendroglioma stem cells, mirroring its requirement for normal NSCs. They used their Sox2flox conditional mutation [70], in combination with the pHGG mouse model [61], to address the effects of Sox2 ablation on tumor reinitiation following tumor cell transplantation into brain. As expected, mice transplanted with SOX2-deleted cells remained tumor-free throughout the time window in which controls developed lethal tumors. Moreover, they showed that loss of tumorigenesis of SOX2-ablated cells was prevented by transduction with a Sox2-expressing virus. From a more practical point of view they demonstrated that vaccination with Sox2 peptides elicited a response that significantly delayed tumor development, underscoring the feasibility of using SOX2 as a target [71].

Among the other SOXB1 members, the role of SOX1 and SOX3 in GBM has not yet been studied but the knockdown of *SOX2* inhibits the expression of SOX1 suggesting that this member might also display a role in this type of neoplasia [68]. Further studies will be necessary to clarify the role of SOX1 and SOX3 in GBM.

Together, all these results underscore the major role that SOX2 displays in the malignant phenotype of GBM.

SOX2 and pediatric tumors

Pathways essential for promoting neural precursor proliferation or growth arrest and differentiation have been implicated in CNS cancers and specifically in pediatric brain tumors; such as Sonic Hedgehog in medulloblastoma [72]. In agreement with this notion, Sox2 is upregulated in pHGG [75] and amplified in several pediatric cell lines [76]. Moreover, high levels of SOX2 are detected in a tissue array of DIPGs, consistent with a role for tumor stem cells in the origin and maintenance of these tumors [77]. SOX2 is also expressed in SHH-associated medulloblastoma with preponderance in adolescent and adult cases [78]. Deciphering the molecular circuitries controlled by Sox2 in pediatric brain tumors could provide insights into these neoplasm development, biology and possible novel molecular targeted therapies.

Table 1. Major discoveries associated to SOX2 protein in CNS tumors

Sox member	Finding	Reference
SOX2-Glioblastoma	sustains stemness properties and tumorigenicity	[55]
	Transcriptional regulation mediated by TGF-β	[56]
	Genetic and Epigenetic modifications	[53]
	Factor responsible for glioblastoma stem cells reprogramming	[57]
SOX2-medulloblastoma	Sustains stemness properties but not involved in tumor survival	[78]
SOX2-oligodendroglioma	Required to maintain stemness properties and tumorigenicity	[71]
SOX4-Glioblastoma	Sustains stemness regulated by TGF-β and modulating SOX2	[56]

SOXB2

SOXB2 group (comprised by SOX14 and SOX21) is closely related to SOXB1. However, SOXB2 factors possess a repression instead of a C-terminal transactivation domain [79] and functionally Sox21 promotes neurogenesis by counteracting the activities of SOXB1 proteins in the developing CNS [80]. The decision of neural precursors to self-renew or to undergo neuronal differentiation therefore depends on the balance of SOXB1 and SOXB2 factors.

Analogous to their opposite roles in development and differentiation, forced expression of SOX21 inhibits SOX2 and induces apoptosis in human glioma cells [81]. Moreover, SOX21 inhibits gliomas progression *in vivo* by forming complexes with SOX2 and stimulating aberrant differentiation [82]. These results imply that SOX21 acts as a tumor suppressor negatively regulating SOX2. They further demonstrate the relevance of the balance between SOXB1 and SOXB2 in tissue homeostasis and disease in the CNS.

SOXC

SOXC proteins are implicated in the biology of different brain tumors [83, 84] with SOX4 and SOX11 exhibiting opposing activities in GBM. On one hand, SOX4 is upregulated in human samples, where it is associated with TGF-β [85], an important signaling pathway in GBM formation and progression [86]. Functionally, the activation of canonical and non-canonical TGF-β signaling enhances GSCs tumor activity through SOX4 protein and consequent boost of SOX2 [56]. Further supporting this axis, inhibition of TGF-β signaling drastically decreases the tumorigenicity of GSCs by promoting their differentiation, and these effects are restored by *SOX2* or *SOX4* re-activation [56]. SOX4 induces the expression of *SOX2* forming cooperative complexes with OCT-4 that bind to the *SOX2* promoter [56]. In addition to their function regulating GSCs, combined high expression of OCT-4, SOX4 and SOX2 confers lower patient survival and correlates with p53-mutated status in GBM cases [87], highlighting the clinical relevance of this axis. Further investigations have revealed that SOX4 acts downstream of miR-204 to suppress GSCs self-renewal [88]. In summary, these findings indicate that SOX4 is a master regulator of GSCs although it remains unresolved whether Sox4 positive cells are the cells of origin of GBM. They also highlight that SOX transcription factors can act sequentially in tumor development, mimicking the action of those in neural lineage development [80].

The role of SOX11 in GBM is less clear. On one hand, SOX11 is transcriptionally overexpressed in GBM [89]; however, low levels correlate with a significant decrease in patient survival [90]. Agreeing with this notion, GSCs have lost SOX11 expression, and its ectopic restoration prevents their tumorigenesis *in vivo* blocking the expression of oncogenic Plagl1 [90]. Moreover, the identification of an immunogenic CD8+ T cell epitope derived from SOX11, which is abundantly and specifically overexpressed in malignant glioma, emphasizes the suitability of this protein for a T cell-based immunotherapy for these patients [91].

SOXE

SOX9 belongs to the related SOXE family and its presence during embryonic development and in adulthood has been associated with stem cell maintenance in the pancreas, hair follicle, breast intestine and CNS [92, 93-95]. In the CNS, Sox9 is essential for gliogenesis and, in conjunction with Sox10, also maintains the

multipotency of neural crest stem cells as well as directing differentiating cells to non-neuronal fates [96]. It acts as a downstream effector of the Shh and Notch pathways [93, 97].

SOX9 expression levels are significantly higher in gliomas than in brain control tissue and increasing WHO grade gliomas display stronger SOX9 staining, together with higher SOX10 [98]. From the clinical point of view, the increased expression of SOX9 in GBM significantly correlates with a lower Karnofsky performance score. In addition, patients with high SOX9 expression present lower disease-free and overall survival rates than those with low SOX9 [99]. Thus, SOX9 expression might be a relevant independent prognostic factor for GBM patients. Other brain tumors such as medulloblastomas and ependymomas also display robust SOX9 expression [84].

Functionally, SOX9 knockdown impairs cell proliferation in glioma cell lines [100], induces the cell arrest in G2/M phase of cell cycle and enhances the apoptosis in glioma cells [99]. The inhibition of its activity mediates the impaired cell cycle progression and reduced cell invasion induced by miR-145 tumor suppressor [101]. In contrast, ectopic expression of SOX9 cooperates to transform NSCs and form tumors with a primitive neuroectodermal tumor profile [40], establishing his functional relevance in the regulation of GSCs (**Figure 1**). Beyond the CNS tumors, Sox9 interacts with pathways and genes also altered in GBM such as EGFR, BMI-1 and PTEN [102-105] and these connections might be interesting to be further investigated in GBM.

Other SOX members might have a prominent role in GBM as well. SOX5 and SOX6 are highly expressed in glioma while are not detected in non-neoplastic tissues [106, 107]. Furthermore, there is a positive correlation between the presence of SOX5 and SOX6 IgGs from the sera of glioma patients and GBM patients survival suggesting they may be useful not only as diagnostic markers, but also as prognostic markers in glioma patients [107]. Finally, SOX17 expression in glioma endothelial cells is related to the angiogenic properties of tumor vessels, suggesting that SOX17 might play a relevant function in GBM promoting tumor angiogenesis and vascular abnormalities [65].

In summary, SOX proteins are differently expressed in GBM with the majority of them inducing aberrant cell growth and promoting tumorigenic activities at various levels. However, their function needs to be further investigated in order to determine whether targeting SOX proteins is a promising therapeutic strategy for GBM in humans.

Future perspectives

SOX factors are critical regulators during embryogenesis playing an integral role in the maintenance of NSCs and lineage differentiation both during embryo development and adult stage. Furthermore, their aberrant expression is observed in malignant gliomas where they exhibit various features of tumorigenesis and tumor progression. SOX2, SOX4 and SOX9 have been consistently shown to act as oncogenes while SOX11 and SOX21 behave as tumor suppressors (**Figure 2**). We have summarized the main role of the different SOX in CNS tumors in **Table 1**. Other members have not displayed a clear function yet.

The outcome of SOX factors activation seems to depend on the tumor origin and cellular context reflecting their roles in different territories during development. They regulate key processes related to tumor biology, including cell proliferation, migration, epithelial mesenchymal transition, angiogenesis, apoptosis, and regulation of GSCs and their opposite roles in these processes could be related to, yet unexplored, regulation of protein activity through transcriptional, post-transcriptional and post-translational events. Future insight into the identification and functional characterization of their downstream target genes in GBM maintenance and progression are needed to determine which SOX may be targeted as a therapeutic strategy for GBM.

Among all the SOX factors, *SOX2* is emerging as a very complex factor with multiple functions (**Figure 3**) not only in transcription but also in chromatin remodelling possibly through its association with the swi/snf complex, NuRD complex and others [108]. Moreover, it has been suggested a role of SOX2 in post-transcription regulation through its association with RNA binding proteins [109] and a putative role as a RNA splicer [110]. These functions have been previously ascribed to central regulator

such as p53 [111]. Nevertheless, further experiments will be necessary to clarify the functional role and the mechanisms of these interactions to understand the complexity of SOX2 networks. This information might indicate that Sox2 targeting should be considered in ongoing efforts to develop novel stem cell targeting therapies. We have ahead of us a very interesting horizon that comes with sophisticated tools such as RNA deep sequencing, ChIRP, RIP-seq, among others, that will allow us to study and decipher the secrets that SOX family members are still hiding. Understanding the underpinnings of these molecular networks would allow proposing tailored therapies against SOX deregulation.

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Disclosure of conflict of interest

None.

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